ABSTRACT

APPLICATIONS OF STOCHASTIC PROCESSES TO CANCER RESEARCH

by

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The purpose of this thesis is to implement stochastic models that are currently used to analyze the impact of different drug treatments on cancer and to model drug resistance by cancer cells. Mathematical models are used to compare single-cancer treatment results with those that involve multiple drugs at the same time. Using various parameters for the model, the probability of treatment success was calculated. A comparison was made with a probability theory approach and good agreement was obtained.

APPLICATIONS OF STOCHASTIC PROCESSES TO CANCER RESEARCH

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CHAPTER 1: Introduction

An application of mathematical modeling to multiple drug cancer treatments is considered. The purpose of such research is to obtain a sufficiently faithful model so that parameters are measurable and meaningful. This can eventually lead to decision making that is based on quantitative feedback from patient data. The purpose of this paper is to use stochastic models to analyze the impact of different drug treatments on cancer and to model drug resistance by cancer cells. The mathematical models compare current single cancer treatments results with combinations of multiple drug treatment results. Using various parameters for the model, the probability of treatment success is calculated. Finding and utilizing different strategies for cancer treatment will improve the chances of treatment success.

There are four main stages of cancer: initiation stage, promoted stage, tumor growth stage, and metastatic stage. Exposure to external substances, as well as the body's natural aging process, can increase the progression of these stages. Chemotherapy is the use of various drugs to slow and/or halt the cancer's development. This study looks at a two-drug cocktail as a treatment strategy and uses both deterministic and stochastic models to analyze the outcomes using EXCEL programs.

Deterministic equations lead to no probability of cure, which is not realistic. On the other hand, the stochastic model actually models the probability of a cure. Stochastic processes are non-deterministic and show a random variable's progression over time. A stochastic process allows a model for estimating the probability of success.

CHAPTER 2: Basic Biological Concepts and Definitions

The progress of cancer involves four main stages. *Initiation* involves changes to the genotype of the cell. To become fully cancerous, a cell must be *promoted*. *Tumor growth* is the result of the excretion of mitogens called vascular endothelial growth factor, *VEGF*, which stimulate the growth of vascular pathways to the cancer cells. At the last stage, cancer becomes *metastatic*, which results in the flow of cells into the blood stream. Exposure to radiation, toxins, viruses, or high concentrations of non-toxic substances can increase the speed of these stages. Natural aging can also lead to changes of states. The protein *p53* is responsible for suppressing cell changes, also called the "guardian of the genome". Its inability to function properly has been connected to the progress of disease. Conversely, excessively high levels of *p53* can result in accelerated aging. See [7], [2], [8], [6], [5].

Various drugs are used to treat cancer and halt cellular advancement to the next stage. This can be done in a series of drug treatments, or all at once in the form of a drug cocktail. A shortcoming with the series approach is that there are cells that are *resistant* to any single drug, and a portion of these will survive and thrive after the first treatment. This opens the opportunity for the disease to progress before the next drug treatment.

The cocktail approach creates an environment whereby a cancer cell must traverse one of several pathways in order to survive the treatment. In this study, cancer cells may die but are assumed not to reproduce during the treatment period.

The various growth and transfer parameters will have one pre-treatment value before the treatment and then their treatment value. During this study, the pre-treatment values will be assumed to be smaller than the treatment values and set to zero. Cells that are not significantly affected by the use of one or more drugs are known as *resistant cells*. In combination therapy or polytherapy, the probability of a cancer cell becoming resistant is independent of the turnover rate. The *turnover rate* is the ratio of natural cell death to the

replication rate of a cancer cell in lack of a treatment. The generation of resistance-mutated cells in the pre-treatment phase strongly depends on the turnover rate when two or more drugs are used. There is also the phenomenon of a cancer cell becoming resistant to the drugs before they are used. This is known as a *pre-existence*. The pre-existence of resistant cells plays an important role on the effectiveness of the treatment in a real clinical setting.

2.1 States and Their Connection with Decay and Mutation Rate Constants

In this thesis, we will closely follow the approach of [7], although the emphasis will be on solving systems of differential eqations. Parameters are denoted in various ways with κ_*, τ_* depending on the processes involved. The decay-rate constants are the rate of cell death due to the treatment and is denoted κ. The states that a single cell can be in are denoted by a vector $\vec{s} \in \mathbb{Z}_2^m$ when m drugs are used, and $\mathbb{Z}_2 = \{0,1\}$ represents the two conditions of being *susceptible*, 0 or *resistant*, 1. Two important states will reappear in our discussion, the fully susceptible (zero) state and the fully resistant (one) state

$$\vec{0} \;=\; \langle 0,0,\ldots,0\rangle \;,\;\; \vec{1} \;=\; \langle 1,1,\ldots,1\rangle \;,$$

respectively. We assume,

$$\kappa_{\vec{s}} > 0 \quad \forall \vec{s} \in (\mathbb{Z}_2)^m - \{\vec{1}\} \;,\;\; \kappa_{\vec{1}} \;=\; 0 \;.$$

What this represents is that every state has the possibility of resulting in the death of cancer cells, except the $\vec{1}$ state, where the cell is fully resistant to all the drugs in the cocktail. The state vector $\vec{s}$ will change *abruptly* over time (ie. changes are *discrete*). What can be modeled *continuously* are the probabilities of being in a state. The number of drugs that a cell is resistant to, at some point in the treatment, is

• number of drug resistances: $\#(\vec{s}) = \vec{1} \cdot \vec{s} = \sum_{i=1}^{m} s_i$,

which gives for the two special cases,

• susceptible to all drugs in the cocktail: $\#(\vec{0}) = 0$

• fully resistant to the treatment: $\#(\vec{1}) = m$.

The mutation or transition-rate constants are denoted by τ. In specific situations, we use the expression τ_a^b to denote the rate of transition from state b to state a. These are characteristics of the relevant drug but also of the type of cancer to which it is being applied. There are important features of the treatment process that we note.

• a cell never transitions back to itself: $\tau_a^a = 0$,

• the treatment cannot make resistant cells susceptible: $\tau_a^b > 0 \implies \tau_b^a = 0$.

As the cells reside in an environment of a drug cocktail, two changes can occur: either the cell dies (with probability proportional to κ), or the cell transforms (with probability proportional to τ). We assume that a transformation occurs from at least a partially susceptible cell, to a cell that is resistant to only one more drug.

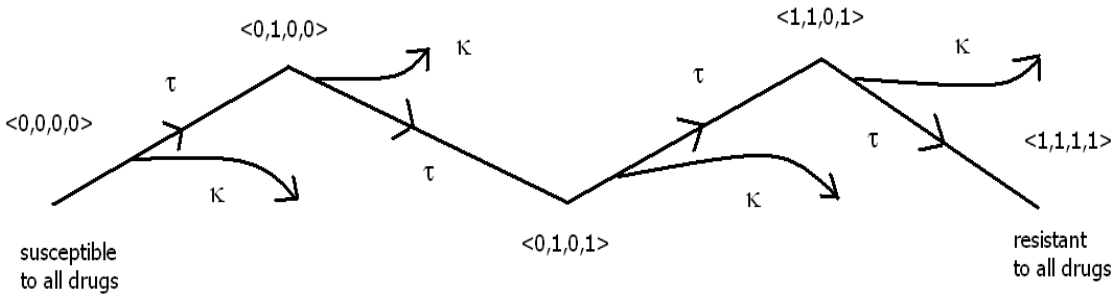

Figure 1: Example path of cells through a 4 drug-cocktail therapy.

The biological aspects that determine the processes of death or mutation are very complex, so they are best dealt with using a statistical approach.

CHAPTER 3: Basic Statistical Concepts and Definitions

In most of this thesis, a basic two-state system is considered. When there are many cells involved, then we work with a string of such states.

Definition 1. A *binary* (base 2) integer is a finite string of 0's and 1's that can be represented as a vector $\vec{s} \in (\mathbb{Z}_2 = \{0,1\})^m$ so that the equivalent *decimal* (base 10) expression is

$$\textbf{binary} \rightarrow \qquad \vec{s} \;=\; \langle s_1, s_2, \ldots\, s_m \rangle \;\equiv\; \sum_{i=0}^{m-1} s_{i+1} \cdot 2^{m-i-1} \qquad \leftarrow \textbf{decimal}\ .$$

Remark 3.1. Example numbers are $0 \equiv 00$, $01 \equiv 1$, $10 \equiv 2$ and $11 \equiv 3$.

To incorporate uncertainty in our study, there is a need for appropriate terminology.

Definition 2. The *sample space* used here is defined to be

$$\Omega \;=\; (\mathbb{Z}_2)^m \;\equiv\; \{\vec{s} = \langle s_1, s_2, \ldots, s_m \rangle \mid s_i \in \mathbb{Z}_2 = \{0,1\}\ \forall i \in \{1,2,\ldots m\}\}\ .$$

Since Ω is finite, the set of possible *events* is the power set

$$\mathcal{P}_2^m \;\equiv\; 2^{\Omega} \;=\; \{\{\vec{s}_1, \ldots \vec{s}_i, \ldots, \vec{s}_k\} \mid \vec{s}_i \in \Omega,\ 0 \leq k \leq m\}\ .$$

Given a probability measure $P : \mathcal{P}_2^m \rightarrow [0,1]$, where

$$P(\emptyset) \;=\; 0,\ P(\Omega) \;=\; 1,\ P(A \cup B) \;=\; P(A) + P(B) - P(A \cap B),$$

Then the triple $\langle \Omega, \mathcal{P}_2^m, P \rangle$ is a probability space.

Next, to model the random nature of the process, we recall the following:

Definition 3. A Markov process is a stochastic process with the following properties:

- the number of possible outcomes or states is finite,
- the outcome at any stage depends only on the outcome of the previous stage,
- the probabilities are constant over time.

These ideas can be extended to a continuous Markov process or chain.

The process we consider takes place in a *combinatorial mutation network*, as described in [7]. In a small time period $\Delta t > 0$, a cancer cell can either (i) remain in its present state, (ii) die due to one of the drugs, or (iii) transform (mutate) into a form that is resistant to one of the drugs in the cocktail. The probability of this occurring is proportional to Δt, but is considered independent of t itself. We ignore the possibility of a cell becoming resistant to two drugs at the same time, or at least within an interval of size Δt.

3.1 Time-varying Probabilities

As the problems considered become more complex, the description for the *state space* Ω must be expanded. Consider the finite sequence $\langle \imath_k \rangle_{k=1}^{N}$ where $\imath_k \in \mathbb{N}_0$ are the numbers of *susceptible* and the number of *resistant* cancer cells in the system of N cells, at some point in time,

$$\Omega \equiv \{ \langle \imath_0, \imath_1 \ldots \imath_N \rangle \mid \imath_k \in \mathbb{N}_0 \} .$$

Susceptible cells have a high likelihood of being killed-off by the use of a drug. Thus, such cells are susceptible to the treatment.

Resistant cells are not significantly affected by the use of one or more drugs. Such cells may survive the entire treatment consisting of a cocktail of drugs.

Let $\pi_{\vec{s}}(t, \imath_{\vec{s}})$ denote the probability $\imath_{\vec{s}} \in \mathbb{N}_0$ of cells of phenotype $\vec{s}$ that are present in the system at time t. For two drugs, the process is modeled as a random walk in 4-dimensional space.

Dummy variables $x_* \in \mathbb{R}$ will be used in the study of this system. In the case of a single-cell system, x_0 corresponds to susceptible cells, and x_1 corresponds to resistant cells. In a two-cell system, there are 4 dummy variables, x_{00}, x_{10}, x_{01} and x_{11} with obvious representation. In the case of $m \in \mathbb{N}$ drugs, we need the notation

$$x_{s_1 s_2 \ldots s_m} \in \mathbb{R} .$$

The use of m is to indicate that this is the number of *mutations* required for the cell to become resistant to the cocktail of m drugs. There are

$$n \equiv 2^m \text{ different phenotypes} ,$$

where $\vec{0}$ corresponds to susceptible to all drugs, and $\vec{1}$ corresponds to resistant to all drugs. Furthermore, there are

$$\binom{m}{k} \text{ different phenotypes resistant to exactly } k \text{ of the drugs} ,$$

for $0 \leq k \leq m$. Our goal is to study the *probability generating function PGF*, Ψ, associated with the treatment process. The *PGF* is similar to the moment generating function, *MGF* used in the study of continuous state spaces. However, since the state space Ω is discrete, we introduce variables $x_* \in \mathbb{R}$, and write

$$\Psi(t; x_{\vec{s}}) = \sum_{\imath_{\vec{s}}} \pi_{\vec{s}}(t; \imath_{\vec{s}}) \cdot \prod_k x_k^{\imath_{\vec{s}_k}} . \tag{3.1}$$

This is a multi-variable function, and there are several special cases where information can

be easily deduced, once it is constructed. For instance,

$$\Psi(t;\vec{1}) \;=\; \sum_{\imath_{\vec{s}}} \pi_{\vec{s}}(t;\,\imath_{\vec{s}}) \;=\; 1\;,$$

as must be the case for probabilities.

3.2 Probability Generating Functions

A *generating function* for a discrete random variable S, that has possible values $s_n \in \mathbb{R}$ for $n \in \mathbb{N}$, is a series expressed in term of a dummy variable, t. A *probability generating function PGF*, can only be used with discrete integral distributions. The most common distributions are the binomial, the Poisson, and the geometric. See [11]. The random variable S in the distribution can take only non-negative integer values. The *PGF* is defined by

$$\Psi_s(t) \;\equiv \sum_{n=0}^{\infty} P\,(S = s_n)\,t^n\;, \tag{3.2}$$

where $P(S=s)$ is the probability of S taking on the value s. A simple example of a *PGF* is as follows: let the random variable S be defined by

$$S \;=\; \begin{cases} 1 & \text{if the outcome is a success}\;, \\ 0 & \text{if the outcome ends in a failure}\,. \end{cases}\;.$$

The *PGF* can be expressed in terms of moments, which leads to another type of generating function called a *moment generating function*, *MGF*. *MGFs* can be used with both discrete and continuous distributions, and are therefore less restrictive than *PGFs*. See [11].

MGFs are defined for a random variable X, in terms of a real number t, by

$$M_x(t) = E[e^{tx}] \; = \; \begin{cases} \sum e^{tx} f(x) & \text{if X is discrete ,} \\ \int_{-\infty}^{\infty} e^{tx} f(x) dx & \text{if X is continuous .} \end{cases} . \tag{3.3}$$

While moment generating functions are very useful, probability generating functions are used in this study. Here the two states for S are:

$$success = susceptible \quad , \quad failure = resistant.$$

3.2.1 Two Coin-Toss Model

Consider the example of tossing two coins where the possible outcomes are

$$s \; \in \; \{HH, TH, HT, TT\} \; \equiv \; \{0, 1, 2\} \, ,$$

but the order is unimportant. Letting $H \equiv 0$ and $T \equiv 1$ we obtain the *PGF*

$$\Psi_{any\ order}(x) \; = \; \sum \pi_s \prod x^s \; = \; 0.25 \; + \; 0.5x \; + \; 0.25x^2 \; = \; (1+x)^2/4 \, ,$$

for $x \in [0, 1]$. This leads to two identities

$$\Psi(0) \; = \; P(No \text{ “}T\text{”}) \; = \; 0.25 \, , \;\; \Psi(1) \; = \; 1 \, .$$

However, there are more identities involving the derivatives of the *PGF*:

$$\Psi'(1) \; = \; Mean \; = \; 1 \, , \;\; \Psi''(1) + \Psi'(1) - \left(\Psi'(1)\right)^2 \; = \; Var \; = \; 0.5 \, .$$

Conversely, suppose order is important in the two-coin toss experiment. Then the pos-

sible outcomes are

$$s \in \{HH, TH, HT, TT\} \equiv \{00, 01, 10, 11\} ,$$

Then the associated *PGF* is

$$\Psi_{order\ important}(x,y) = 0.25 + 0.25x + 0.25y + 0.25xy = (1+x)(1+y)/4 ,$$

which gives the obvious identities

$$\Psi(0,0) = P(No\text{“}T\text{”}) = 0.25 , \ \Psi(1,1) = 1 ,$$

but also identities involving partial derivatives:

$$\partial_x \Psi(1,1) = P(y = H | x = H) = 0.5 .$$

3.3 Kolmogorov Forward Equation

A discrete stochastic process $\{S_n\}_{n\in\mathbb{Z}}$, where the S_n take their values in a sample space $\mathcal{S}$, is Markovian if the statistics of S_n depend only on the value of S_{n-1}. For any $r \in \mathbb{R}$, this can be expressed as

$$P(S_n \leq r \mid s_{n-1}, s_{n-2}, \dots) = P(S_n \leq r \mid s_{n-1}) .$$

Now, if we had all information on these conditional probabilities, then we could compute the probability

$$P(S_n \leq r) = \sum_{s_{n-1}\in\mathcal{S}} P(S_n \leq r \mid s_{n-1}) P(s_{n-1}) .$$

These are the Chapman-Kolmogorov equations. For our application, these equations were used for computing n^{th}-step transition probabilities P_{ij}^n from a state i to a state j. In this setting, the equations take the form

$$P_{ij}^{n+m} \;=\; \sum_{k=0}^{\infty} P_{ik}^n \, P_{kj}^m \;, \quad \text{for all}\, n,m \geqslant 0, \forall i,j \in \mathbb{N}_0 \;. \tag{3.4}$$

The Kolmogorov Forward Equation and Backward Equation are derived from (3.4) by allowing n and m to be continuous variables. In particular, let $m = \Delta t > 0$ be a small real number. Then subtracting P_{ij}^n from both sides gives

$$P_{ij}^{n+\Delta t} - P_{ij}^n \;=\; \sum_{k=0}^{\infty} P_{ik}^n \, \left(P_{kj}^{\Delta t} \;-\; P_{kj}^0 \right) \;, \tag{3.5}$$

where $P_{kk}^0 = 1$ but $P_{kj}^0 = 0$ for $k \neq j$. See [12]. (Note, this condition is also written as $P_{kj}^0 = \delta_k^j$ where δ_k^j is the Kronecker delta so that $\delta_k^k = 1$ and vanishes otherwise.) Dividing both sides by $\Delta t > 0$ and taking the limit as $\Delta t \to 0$, equation (3.5) becomes a differential equation. Let $n = t \in \mathbb{R}_0^+$. Then we have the system of ordinary differential equations, *ODEs*, for the $P_{ij}(t)$ functions,

$$P_{ij}'(t) \;=\; \sum_{k=0}^{\infty} P_{ik}(t) \, P_{kj}'(0) \;, \tag{3.6}$$

for $t \geq 0$. Now, we see that the rates of change depend on information only at $t = 0$, so they are time-independent. Thus (3.6) is a constant-coefficient *ODE* where we denote

$$\kappa_i \;=\; -P_{ii}'(0) \;\geq\; 0 \qquad \text{and} \qquad \tau_j^{\,k} \;=\; P_{kj}'(0) \;.$$

This gives the Kolmogorov Forward Equations *KFE* in the form

$$P_{ii}'(t) \quad = \quad \sum_{k \neq i} \tau_i^k \, P_{ik}(t) \;-\; \kappa_i \, P_{ii}(t) \tag{3.7}$$

$$P'_{ij}(t) \quad = \quad \sum_{k\neq i,j} \tau^k_j P_{ik}(t) \; - \; \kappa_j P_{ij}(t) \; + \; \tau^i_j P_{ii}(t) \; . \tag{3.8}$$

In physical applications this is sometimes called the Fokker-Planck Equation and in biology it is called the Chemical Master Equation. We use the *KFE* later in the study when working with stochastic differential equations.

3.4 Stochastic Differential Equations

To understand data that is generated from a random process, one needs to have probability distributions π_* that model the output. When the distributions $\pi_*(t)$ change over time they satisfy a *KFE* written in generality as

$$\frac{d\pi_I}{dt} \; = \; \sum_{I_-} K^I_- \cdot I_- \cdot \pi_{I_-} \; + \; K^I_0 \cdot I \cdot \pi_I \; + \; \sum_{I_+} K^I_+ \cdot I_+ \cdot \pi_{I_+} \; , \tag{3.9}$$

for coefficients K_* that depend on the process. Here I_- corresponds to preceding states, and I_+ forthcoming states. Also, $K_0 \leq 0$ is required for stability.

For the *KFE* in (3.9) a dummy variable $x \in [0,1]$ is introduced. A probability density function, *PDF*, is constructed from equation (5.10),

$$\Psi(t;x) \; \equiv \; \sum_I \pi_I(t) \cdot \prod x^I \; . \tag{3.10}$$

To determine expectations, one can apply a *partial differential operator PDO*, to the *PDF*. For example

$$\left(x_{I_*} \partial_{x_{I_*}} \Psi\right)(t;\vec{1}) \; = \; \langle I_* \rangle_t \; ,$$

is the time-varying expectation of the s_* random variable. Taking the time derivative of

(3.10) and using equation (3.9) gives a system of partial differential equations, *PDEs*,

$$\frac{\partial \Psi}{\partial t} = \vec{v} \cdot \nabla \Psi \,, \tag{3.11}$$

where the components $\vec{v}_*$ are quadratic polynomials in x. Since this equation is *hyperbolic* and *first order*, one can use the method of characteristics to write a system of *ODEs* to solve the *PDEs*.

CHAPTER 4: Strategies of Numerical Analysis

4.1 Ordinary Differential Equations

Consider a differentiable t-varying vector of variables $\vec{x}(t)$ with values in $\mathbb{R}^n$. The rate of change vector $\vec{F}$ may depend on t explicitly, and it may depend on $\vec{x}$, which is an implicit dependence on t (the only independent variable). A system of *ordinary differential equations*, *ODEs*, is given by

$$\frac{d\vec{x}}{dt} \equiv \vec{x}'(t) = \vec{F}(t;\vec{x}(t)) \equiv \vec{F}(t;\vec{x}) \ . \tag{4.1}$$

When $\vec{F}$ does not depend on t explicitly, then equation (4.1) is called *autonomous* expressed as $\vec{F} = \vec{F}(\vec{x})$. When $\vec{F}(t;\vec{x}) = M(t)\vec{x}$ for some $n \times n$ matrix M with continuously varying components, then equation (4.1) is called *linear*.

This thesis will work with constant $n \times n$ matrices M in which case equation (4.1) is an n-dimensional *constant coefficient system* of *ODEs*. Given initial conditions $\vec{x}_0 \in \mathbb{R}^n$ there is a unique solution $\vec{x}(t)$, at least on some interval $[0,T]$. In particular,

$$\frac{d\vec{x}}{dt} = M\vec{x} \text{ and } \vec{x}(0) = \vec{x}_0 \implies \vec{x}(t) = \exp[Mt]\,\vec{x}_0 \ . \tag{4.2}$$

Using a Taylor expansion, the solution can be written as

$$\vec{x}(t) = e^{Mt}\vec{x}_0 = \sum_{k=0}^{\infty} \frac{t^k}{k!} M^k \cdot \vec{x}_0 = \vec{x}_0 + tM\vec{x}_0 + (t^2/2)M^2\vec{x}_0 + O(t^3) \ . \tag{4.3}$$

We do not focus on the variety of solutions that one obtains. See [1]. However, the matrices considered here do have the special property that the sum of their columns equals 0. This encodes the conservation of probabilities when applied to Markov processes.

4.2 First-Order Partial Differential Equations

An equation that relates an unknown function of two or more *independent* variables to its partial derivatives is called a *partial differential equation*, *PDE*. The study of such equations is a continuing area of research. Non-linear *PDEs* are particularly difficult to solve.

We start with the simple case of a general *first-order linear, non-homogeneous PDE*, which takes the form,

$$A(x,y)\frac{\partial u}{\partial x} + B(x,y)\frac{\partial u}{\partial y} + C(x,y)u = R(x,y) . \tag{4.4}$$

If $A(x,y)$ or $B(x,y)$ are equal to zero then the *PDE* can be reduced to a first order *ODE*. See [11].Otherwise, one can use the *method of characteristics* to reduce (4.4) to a system of *ODEs*. See [3]. This works by artificially introducing a variable t and assuming that $u(x,y) = u(x(t),y(t))$. Then, taking the full derivative in t gives

$$\frac{du}{dt} = \frac{dx}{dt}u_x + \frac{dy}{dt}u_y . \tag{4.5}$$

Now, comparing (4.4) and (4.5) gives the system of *ODEs*

$$\frac{dx}{dt} = A(x,y) , \ \frac{dy}{dt} = B(x,y) , \ \frac{du}{dt} = R(x,y) - C(x,y)u . \tag{4.6}$$

The price that one pays for this conversion to (4.6) is that the linear *PDE* in (4.4) is now a system of non-linear (in general) *ODEs*.

Example 4.1. Consider the *linear non-homogeneous PDE*

$$yu_x + 6u_y = x + y , \ u(x,0) = x+2 . \tag{4.7}$$

The *method of characteristics* gives the system of *ODEs*

$$\frac{dx}{dt} = y\,, \quad \frac{dy}{dt} = 6\,, \quad \frac{du}{dt} = x + y\,. \tag{4.8}$$

It is best to start with the middle equation, which gives

$$y(t) = 6t + y_0\,,$$

where $y_0 \in \mathbb{R}$ is an arbitrary constant. However, if the characteristic line $y = 0$ is forced to correspond to $t = 0$, then $y_0 = 0$,in which case $y(t) = 6t$. This is substituted into the first equation to give

$$x(t) = 3t^2 + x_0\,,$$

and since x varies along the characteristic, we allow $x_0 \in \mathbb{R}$. This can now be inserted into the third equation to give

$$u' = 3t^2 + x_0 + 6t \implies du = (3t^2+6t+x_0)\,dt \implies u(t) = t^3+3t^2+x_0t+C\,.$$

The choice of the arbitrary constant C will help to understand the solution. In particular, let $C = u_0$. Then, using the *Cauchy data*: $u(x,0) = x+2$, immediately gives $u_0 = x_0 + 2$.Combining $u(t)$ and $x(t)$ gives

$$\begin{aligned} u(t) &= t^3 + 3t^2 + x_0t + x_0 + 2 \\ &= -2t^3 + (3t^2+x_0)t + (3t^2+x_0) + 2\,. \end{aligned}$$

Now, using $t = y/6$ and $x = 3t^2+x_0$, we obtain

$$u(x,y) = -2(y/6)^3 + xy/6 + x + 2\,.$$

It is easy to check that $u(x,y)$ solves equation (4.7).

Linear *PDEs* are not so easy to solve in general and sometimes we need to solve the system of *ODEs* in (4.8) in order to solve the corresponding *PDE*. A simplification occurs for homogeneous *PDEs*.

Example 4.2. Consider the *linear homogeneous PDE*

$$y u_x + 6 u_y = 0 , \;\; u(x,0) = x+2 . \tag{4.9}$$

Again, the method of characteristics gives the simple system of *ODEs*

$$\frac{dx}{dt} = y , \;\; \frac{dy}{dt} = 6 , \;\; \frac{du}{dt} = 0 . \tag{4.10}$$

The middle equation gives $y(t) = 6t$, the first equation gives $x(t) = 3t^2 + x_0$, and the last equation simply gives $u(t) = u_0$. The *Cauchy data* implies $u(x,0) = x+2$, or simply $u_0 = x_0 + 2$. Combining $u(t)$ and $x(t)$ gives

$$\begin{aligned} u(t) &= u_0 \\ &= x_0 + 2 \\ &= x - 3t^2 + 2 , \end{aligned}$$

which, upon elimination of t using $t = y/6$, gives

$$u(x,y) = x - y^2/12 + 2 .$$

This solves equation (4.9). However, along the parameterized characteristic curve

$$\gamma_{(x_0,0)}(t) = (x(t), y(t)) = \left(3t^2 + x_0, 6t\right) , \;\; t \in \mathbb{R} \qquad \text{or simply: } x = y^2/12 + x_0 ,$$

the solution $u(x,y)$ is a constant, with value

$$u|_{\gamma_{(x_0,0)}} = u_0 = x_0 + 2 .$$

Thus the characteristic curves $\gamma_{(x_0,0)}$ contain a lot of information about the *PDE* (4.9).

Comparing the two examples, we see that homogeneous *PDEs* have special properties that are contained in their associated characteristic curves (or simply *characteristics*).

Example 4.3. Finally, consider the *hyperbolic PDE* for solution u in terms of independent variables t, x and y, where

$$y\,u_x \,+\, 6\,u_y \;=\; u_t\;,\;\; u(0,x,y) \;=\; x+y+2\;. \tag{4.11}$$

Here the method of characteristics is more complicated, since now we must assume that along a curve

$$\gamma_{(0,x_0,y_0)}(t) \;=\; (t,x(t),y(t))\;,$$

that u can be computed, so that

$$\frac{du|_\gamma}{dt} \;=\; \frac{\partial u}{\partial t} \,+\, \frac{dx}{dt}\,\frac{\partial u}{\partial x} \,+\, \frac{dy}{dt}\,\frac{\partial u}{\partial y} \qquad \Longrightarrow \qquad 0 \;=\; u_t \,-\, y\,u_x \,-\, 6\,u_y\;.$$

giving the equations for γ to be

$$\left.\frac{dx}{dt}\right|_\gamma \;=\; -y\;,\;\; \left.\frac{dy}{dt}\right|_\gamma \;=\; -6\;,\;\; \left.\frac{du}{dt}\right|_\gamma \;=\; 0\;, \tag{4.12}$$

due to (4.11). The middle equation gives $y(t) = -6t + y_0$ and the first equation gives $x(t) = 3t^2 - y_0 t + x_0$. The last equation in (4.12) gives $u(t) = x_0 + y_0 + 2$ using the *Cauchy data* in (4.11)in the form $u(0,x_0,y_0) = x_0 + y_0 + 2$. Combining $u(t)$ and $x(t)$ gives

$$\begin{aligned} u(t,x,y) &= x_0 \,+\, y_0 \,+\, 2 \\ &= \big(x \,-\, 3t^2 \,+\, (y+6t)\,t\big) \,+\, (y \,+\, 6t) \,+\, 2 \\ &= x \,+\, (t+1)\,y \,+\, 3t^2 \,+\, 6t \,+\, 2\;, \end{aligned}$$

which solves the *PDE* in (4.11). The parameterized characteristic curve, along which u

is the constant $u_0 = x_0 + y_0 + 2$, is given by

$$\gamma_{(0,x_0,y_0)}(t) \;=\; (t, x(t), y(t)) \;=\; \left(t,\; 3t^2 - y_0 t + x_0,\; -6t + y_0\right) \;,\;\; t \in \mathbb{R}\,.$$

Knowledge of γ provides a way to understand the solution u.

It will be seen that the *PDF* is constant along characteristics, and thus the asymptotes of the probability distributions can be determined with relative ease.

4.3 Euler's Method for solving ODEs

Euler's method is used to solve differential equations by considering an associated difference scheme whose limit for small changes gives differentiation. It is only a first-order method with regards to errors, and so Euler's Method is often considered to be too unstable for practical applications. However, the equations considered here are linear and the solutions are bounded. Thus, for the most part, Euler's method is used within an EXCEL spreadsheet program.

Suppose that $\vec{F} : \mathcal{N}_\varepsilon^{n+1} \to \mathbb{R}^n$ is continuous in all variables in an ε-neighborhood of $(0, \vec{x}_0)$, denoted

$$\mathcal{N}_\varepsilon^{n+1} \;\equiv\; (-\varepsilon, \varepsilon) \times \mathcal{M}_\varepsilon^n \subset \mathbb{R}^{n+1} \;\text{ where } \mathcal{M}_\varepsilon^n \;\equiv\; \left(\vec{x}_0 + (-\varepsilon, \varepsilon)\vec{1}\right) \;,$$

for some $\varepsilon > 0$. Furthermore, suppose that for each fixed t_0, within ε of 0, the function $\vec{F}(t_0, \cdot) : \mathcal{M}_\varepsilon^n \to \mathbb{R}^n$ is continuously differentiable in a neighborhood of $\vec{x}_0$. Then, given an Initial Value Problem *IVP* for an n-dimensional system of *ODEs*

$$\frac{d\vec{x}(t)}{dt} \;=\; \vec{F}\,(t, \vec{x}(t)) \;,\;\; \vec{x}(0) \;=\; \vec{x}_0 \in \mathbb{R}^n \;, \tag{4.13}$$

has a unique solution. See Theorem 6.4 [4] or [1]. The corresponding Euler method, for small $\Delta t > 0$, takes the form

$$\frac{\Delta \vec{x}_k}{\Delta t} \;=\; \vec{F}(t_k, \vec{x}_k)\;, \quad \text{or} \quad \begin{cases} t_{k+1} \;=\; t_k \;+\; \Delta t \\ \vec{x}_{k+1} \;=\; \vec{x}_k \;+\; \vec{F}(t_k, \vec{x}_k)\,\Delta t \end{cases}\;, \tag{4.14}$$

where $\Delta \vec{x}_k \equiv \vec{x}_{k+1} - \vec{x}_k$. It is well known that as $\Delta t \to 0$ the method becomes increasingly accurate, and converges to the solution of (4.13) on $\mathcal{N}_{\varepsilon}^{n+1}$. However, in practice, the round-off errors accumulate and the computation time increases. See [13]. A comparison is made using a higher order method, and the results are given in the appendix.

4.4 Runge-Kutta Method for solving ODEs

There are various orders of Runge-Kutta methods that can be used to numerically integrate the system in (4.13). The popularity of this approach is because it does not require differentiating $\vec{F}$, unlike the higher-order Taylor methods [10]. The second order method used here, referred to as *RK2*, involves a step-by-step process that provides an approximation for $\vec{x}_{i+1}$, as with the Euler method, but uses mid-point information, giving

$$\begin{cases} t_{k+1} \;=\; t_k \;+\; \Delta t \\ \vec{x}_{k+1} \;=\; \vec{x}_k \;+\; \vec{F}\left(t_k + \Delta t/2,\; \vec{x}_k + \vec{F}(t_k, \vec{x}_k)\Delta t/2\right)\,\Delta t \end{cases}\;. \tag{4.15}$$

A comparison between Euler's method and *RK2* is given in the appendix. In the special case that $\vec{F}(t, \vec{x}) = M\vec{x}$, for a constant coefficient $n \times n$ matrix M, then

$$\vec{x}_{k+1} \;=\; \vec{x}_k \;+\; \Delta t\, M \cdot \vec{x}_k \;+\; (\Delta t^2/2)\, M^2 \cdot \vec{x}_k\;,$$

which contains three terms in the Taylor expansion of $e^{M\Delta t}$, as shown in (4.3). This explains why *RK2* is a second-order method in Δt.

4.5 Numerical solution for a deterministic model of chemotherapy

Time, $t \in [0, 100]$, is the only independent variable. The number of cancer cells of different types, I_*, is the main dependent variable. A cell-type may be *susceptible* or sensitive to a drug, or may be *resistant* or immune to a drug. An application of a treatment cocktail, represented by a rate vector $\vec{\kappa}$, is expected to cause many initial cancer-cell deaths. However, another possible process can occur, represented by rate vector $\vec{\tau}$, where some susceptible cancer cells transform into drug resistant cells. A simple form of the system of ordinary differential equations *ODEs* is

$$\frac{d\vec{I}}{dt} \;=\; -diag(\vec{\kappa})\vec{I} \,+\, \vec{\tau}\,. \tag{4.16}$$

If $\vec{\tau}$ linearly depends on $\vec{I}$ and is independent of t, then a unique solution is easy to find. In this case, $\vec{\tau} = T \cdot \vec{I}$ for a square matrix T. A weakness of this model is that it always predicts the survival of some cancer cells. Therefore, no treatment could ever be successful.

Here $0 = s \equiv susceptible$ and $1 = r \equiv resistant$. Writing equation (4.15) as a matrix system, one has

$$\frac{d\vec{I}}{dt} \;=\; -K \cdot \vec{I} \,+\, T \cdot \vec{I}\,,$$

where the 4×4 evolution matrices are

$$K = \begin{pmatrix} \kappa_0 & 0 & 0 & 0 \\ 0 & \kappa_1 & 0 & 0 \\ 0 & 0 & \kappa_2 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \;,\; T = \begin{pmatrix} -\tau_1{}^0 - \tau_2{}^0 & 0 & 0 & 0 \\ \tau_1{}^0 & -\tau_3{}^1 & 0 & 0 \\ \tau_2{}^0 & 0 & -\tau_3{}^2 & 0 \\ 0 & \tau_3{}^1 & \tau_3{}^2 & 0 \end{pmatrix} .$$

Note that setting $\kappa_3 = 0$ models the loss of effectiveness of the treatment for the I_3-type

cells (cancer cells resistance to both drugs). As is required for a transition or stochastic matrix, the sum of each column in T vanishes. Also, the T matrix is lower triangular, which indicates that a resistant cell cannot become susceptible. The total number of cells is given by

$$N(t) \equiv I_0(t) + I_1(t) + I_2(t) + I_3(t) \,, \tag{4.17}$$

which decreases over time, but approaches a constant asymptote.

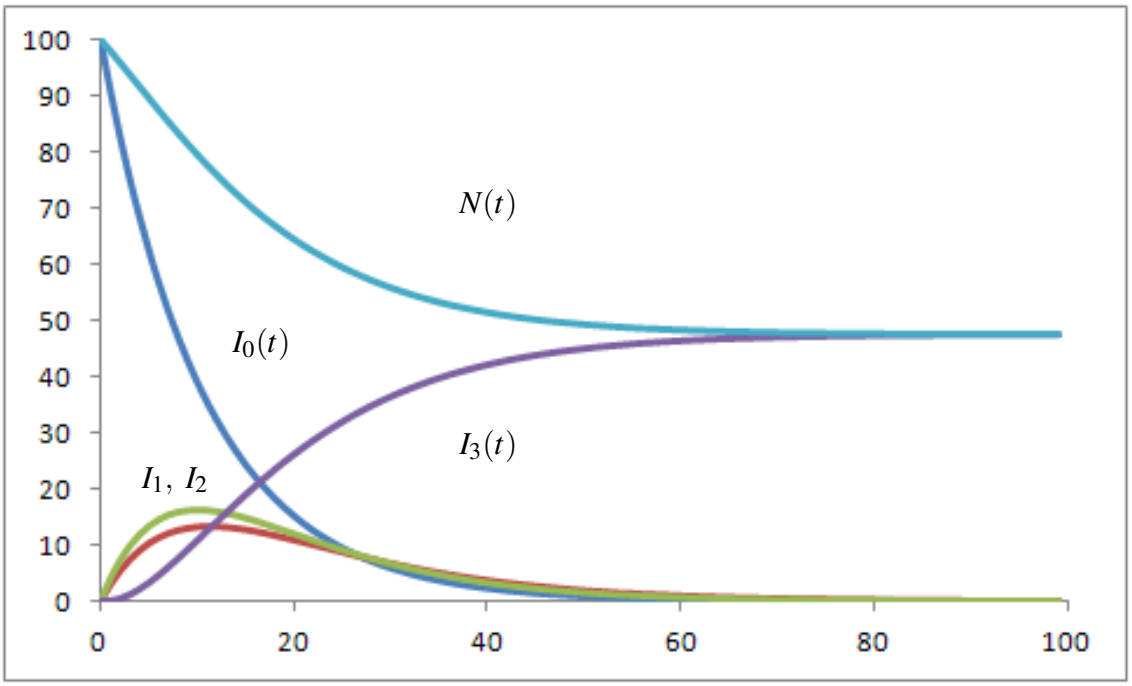

Figure 2: Numerical solutions for deterministic model (I_0, I_1, I_2, I_3, N).

We solve equation (4.15) numerically for a two-drug cocktail starting with initial conditions:

$$I_0(0) = 100 \,, \;\; I_1(0) = I_2(0) = I_3(0) = 0 \,. \tag{4.18}$$

The decay rate parameters are set to

$$\kappa_0 \;=\; 0.02 \,, \;\; \kappa_1 \;=\; 0.03 \,, \;\; \kappa_2 \;=\; 0.04 \,. \tag{4.19}$$

and the transition rates are set to

$$\tau_1^0 = 0.03\,,\ \tau_2^0 = 0.04\,,\ \tau_3^1 = 0.05\,,\ \tau_3^2 = 0.06\,. \tag{4.20}$$

Parameters are chosen so that the treatment time is short compared with the cancer-cell growth rate. The conclusion is that half of the cells survive, thus no remission is possible.

Remark 4.4. The square matrix $M = -K + T$ has the properties:

- The diagonal elements are non-positive;
- The matrix is lower triangular.

These ensure that the eigenvalues are non-positive, and thus the system does not grow exponentially.

CHAPTER 5: Two-Drug Cocktail as a Treatment Strategy

When a series of drugs are administered, the actual microscopic responses of the susceptible cancer cells are very difficult to model. In practice, one is really just interested in the effectiveness of the treatment. To understand the process, we consider increasing levels of complexity. This will help to establish notation and definitions.

5.1 Two-Drug Treatment, One-Cell System

Consider a chemotherapy involving two drugs. A cancer cell can be in one of four states during a treatment, if it has not yet died, expressed as:

$$\vec{s}_0 \equiv \begin{pmatrix} 0 \\ 0 \end{pmatrix} = \begin{pmatrix} s \\ s \end{pmatrix} \ , \ \vec{s}_1 \equiv \begin{pmatrix} 0 \\ 1 \end{pmatrix} = \begin{pmatrix} s \\ r \end{pmatrix} \ , \ \vec{s}_2 \equiv \begin{pmatrix} 1 \\ 0 \end{pmatrix} = \begin{pmatrix} r \\ s \end{pmatrix} \ , \ \vec{s}_3 \equiv \begin{pmatrix} 1 \\ 1 \end{pmatrix} = \begin{pmatrix} r \\ r \end{pmatrix} \ . \quad (5.1)$$

Here $0 = s \equiv susceptible$ and $1 = r \equiv resistant$. It is assumed that a cell transforms or dies discretely, meaning that there is some non-zero time between changes of state. An unknown in this process is the time between different states, and this is what has to be modeled in the stochastic approach. Paths involving no cancer deaths is given in Figure 3.

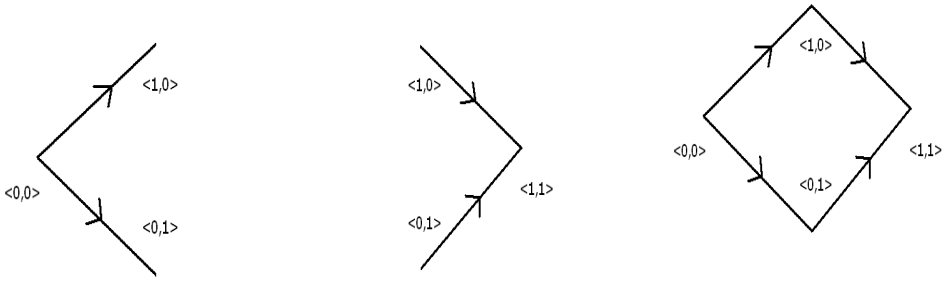

Figure 3a First change of state; **3b** Second change; **3c** Combined changes.

Consider a single cancer cell being treated with a cocktail of two drugs for $t \geq 0$. The probability that it is in a susceptible state at time t is denoted $\pi_{\langle 0 \rangle}(t)$, and this probability changes according to the equation

$$\begin{aligned} \pi'_{\langle 0 \rangle}(t) &= -\kappa_{0,1} \cdot \pi_{\langle 0 \rangle}(t) - \kappa_{0,2} \cdot \pi_{\langle 0 \rangle}(t) \\ &\quad - \tau_1^0 \cdot \pi_{\langle 0 \rangle}(t) - \tau_2^0 \cdot \pi_{\langle 0 \rangle}(t) . \end{aligned} \tag{5.2}$$

The death rate will be combined into a single constant $\kappa_0 \equiv \kappa_{0,1} + \kappa_{0,2}$. The model in (5.2) suggests that the single cell will not remain susceptible and so must decay into one of the other states if it does not die. Becoming susceptible to drug 1 is modeled by

$$\begin{aligned} \pi'_{\langle 1 \rangle}(t) &= -\kappa_{1,3} \cdot \pi_{\langle 1 \rangle}(t) \\ &\quad + \tau_1^0 \cdot \pi_{\langle 0 \rangle}(t) - \tau_3^1 \cdot \pi_{\langle 1 \rangle}(t) . \end{aligned} \tag{5.3}$$

Similarly, for drug 2 one obtains the equation

$$\begin{aligned} \pi'_{\langle 2 \rangle}(t) &= -\kappa_{2,3} \cdot \pi_{\langle 2 \rangle}(t) \\ &\quad + \tau_2^0 \cdot \pi_{\langle 0 \rangle}(t) - \tau_3^2 \cdot \pi_{\langle 2 \rangle}(t) . \end{aligned} \tag{5.4}$$

The final differential equation is for the probability of resistance to both drugs,

$$\pi'_{\langle 3 \rangle}(t) = +\tau_3^1 \cdot \pi_{\langle 1 \rangle}(t) + \tau_3^2 \cdot \pi_{\langle 2 \rangle}(t) . \tag{5.5}$$

There remains to consider the desired state of the system, which is the situation where there is no cancer cell. The probability of this at time t is denoted $\pi_{\emptyset}(t)$ and satisfies

$$1 = \pi_{\langle 0 \rangle}(t) + \pi_{\langle 1 \rangle}(t) + \pi_{\langle 2 \rangle}(t) + \pi_{\langle 3 \rangle}(t) + \pi_{\emptyset}(t) . \tag{5.6}$$

Taking the derivative of both sides, rearranging, and using equations (5.2)-(5.5)gives:

$$\pi'_{\emptyset}(t) = \kappa_{0,1} \cdot \pi_{\langle 0 \rangle}(t) + \kappa_{1,3} \cdot \pi_{\langle 1 \rangle}(t) + \kappa_{2,3} \cdot \pi_{\langle 2 \rangle}(t) . \tag{5.7}$$

We can now combine these equations into a 5-dimensional system of *ODEs*

$$\frac{d}{dt}\begin{pmatrix}\pi_{\langle 0\rangle}\\ \pi_{\langle 1\rangle}\\ \pi_{\langle 2\rangle}\\ \pi_{\langle 3\rangle}\\ \pi_{\emptyset}\end{pmatrix} = \begin{pmatrix}-\kappa_0-\tau_1^0-\tau_2^0 & 0 & 0 & 0 & 0\\ \tau_1^0 & -\kappa_{1,3}-\tau_3^1 & 0 & 0 & 0\\ \tau_2^0 & 0 & -\kappa_{2,3}-\tau_3^2 & 0 & 0\\ 0 & \tau_3^1 & \tau_3^2 & 0 & 0\\ \kappa_0 & \kappa_{1,3} & \kappa_{2,3} & 0 & 0\end{pmatrix}\cdot\begin{pmatrix}\pi_{\langle 0\rangle}\\ \pi_{\langle 1\rangle}\\ \pi_{\langle 2\rangle}\\ \pi_{\langle 3\rangle}\\ \pi_{\emptyset}\end{pmatrix}. \tag{5.8}$$

Remark 5.1. The generator of (5.8) has the properties that:

- The diagonal elements are non-positive;
- The off-diagonal elements are non-negative;
- The sum of each columns is zero.

The consequence is that the sum of the probability five-component vector

$$\vec{\pi}(t) \equiv (\pi_{\langle 0\rangle} \quad \pi_{\langle 1\rangle} \quad \pi_{\langle 2\rangle} \quad \pi_{\langle 3\rangle} \quad \pi_{\emptyset})^T \tag{5.9}$$

is a constant. Using the initial condition

$$\vec{\pi}(0) \equiv (1 \quad 0 \quad 0 \quad 0 \quad 0)^T , \tag{5.10}$$

we see that $\#(\vec{\pi}(t)) = \#(\vec{\pi}(0)) = 1$ for all $t \geq 0$.

Theorem 5.2. *Let M be a constant coefficient square matrix, whose columns add to 0. Then the linear ODE: $\vec{y}' = M\vec{y}$, with $\vec{y}(0) = \vec{y}_0 \in \mathbb{R}$, has a solution $\vec{y}(t)$ where the sum of its components are constant.*

Proof. First note that $\#(\vec{y}) = \vec{1}^T \cdot \vec{y}$. Thus, applying $\vec{1}^T$ to the left of the ODE gives,

$$\#\vec{y}(t)' = \left(\vec{1}^T \cdot \vec{y}\right)' = \vec{1}^T \cdot \vec{y}' = \vec{1}^T \cdot M \cdot \vec{y} = \left(M^T \cdot \vec{1}\right)^T \cdot \vec{y} = \vec{0} \cdot \vec{y} = 0 .$$

Here we used that $\vec{1}^T \cdot M = \vec{0}$, meaning that the sum of the columns of M vanishes. □

A plot of the numerical solution to the *IVP* in (5.9) with Initial Condition (5.9) is identical with that of Figure 2 except that $\pi_{\emptyset}(t) = 1 - N/100$. The corresponding *PGF* is simply

$$\Psi(t;x_1,x_2) \;=\; \pi_{\langle 0\rangle}\cdot x_0 \;+\; \pi_{\langle 1\rangle}\cdot x_1 \;+\; \pi_{\langle 2\rangle}\cdot x_2 \;+\; \pi_{\langle 3\rangle}\cdot x_3 \;+\; \pi_{\emptyset}\;.$$

Once constructed, the *PGF* can be used to derive the probabilities using partial derivatives and substitution:

$$\pi_{\langle j\rangle}(t) \;=\; \frac{\partial\Psi(t;x_1,x_2)}{\partial x_j}\;,\;\; \pi_{\emptyset}(t) \;=\; \Psi(t;0,0)\;.$$

The goal of any treatment is to make $\lim_{t\to\infty}\Psi(t,0,0)$ as close to 1 as possible.

5.2 Two-Drug Treatment for a Two-Cell System

When there is more than one cancer cell in the system, our perspective must change from the deterministic perspective. Suppose a 2-drug treatment is begun at $t = 0$ and ends at $t = T$. Each cell can be in one of four states 0, 1, 2 and 3, where

- 0: both cells are susceptible to both drugs,
- 1: one cell is resistant and one cell is susceptible,
- 2: one cell is resistant and one cell is susceptible,
- 3: both cells are resistant to both drugs.

The set of different states of the system are given by the following two methods

$$\begin{aligned}\Big\{\quad & \langle 3,3\rangle = 20,\ \langle 3,2\rangle = 19,\ \langle 3,1\rangle = 18,\ \langle 3,0\rangle = 17,\\ & \langle 2,3\rangle = 16,\ \langle 2,2\rangle = 15,\ \langle 2,1\rangle = 14,\ \langle 2,0\rangle = 13,\\ & \langle 1,3\rangle = 12,\ \langle 1,2\rangle = 11,\ \langle 1,1\rangle = 10,\ \langle 1,0\rangle = 9,\\ & \langle 0,3\rangle = 8,\ \langle 0,2\rangle = 7,\ \langle 0,1\rangle = 6,\ \langle 0,0\rangle = 5,\\ & \qquad \langle 3\rangle = 4,\ \langle 2\rangle = 3,\ \langle 1\rangle = 2,\ \langle 0\rangle = 1,\ \langle\,\rangle = 0\quad\Big\}\;,\end{aligned} \tag{5.11}$$

which are found to be convenient for both the theoretical and numerical work. Counting elements in this set identifies 21 different states. However, some states are considered

equivalent, or in the same class, since the order is not important. For example,

$$\langle 2,1\rangle = 14 \sim \langle 1,2\rangle = 11 \ .$$

By inspection of (5.11) the actual number of different states is found to be 15. At $t = 0$ the system is in the

$$\text{initial state} \ \equiv \ \langle 0,0\rangle = 5 \ ,$$

and as $t \to \infty$ the system will most likely be in either

$$\text{resistant states} \ \to \ \langle 3,3\rangle = 20 \ , \text{ or } \langle 3\rangle = 4 \ ,$$

or the most desirable situation

$$\text{disease-free state} \ \equiv \ \langle\,\rangle = 0 \ .$$

As in the one-cell case, we associate probabilities to the possible states of the system. Each cell can be in one of four states $0,\ 1,\ 2$ and 3, as discussed in the one-cell case. Now we create a function

$$\iota_j \ \to \ \#\text{ cells of type } j \ \text{ for } j \in \{0,\ 1,\ 2,\ 3\} = \mathbb{Z}_4 \ .$$

In the 2-cell case the range of ι_j is $\mathbb{Z}_3 = \{0,\ 1,\ 2\}$. The notation that will be employed is for the probabilities is

$$\pi_{\iota_0,\iota_1,\iota_2,\iota_3} \ \text{ so that } \ 0 \le \iota_0 + \iota_1 + \iota_2 + \iota_3 \le 2 \ , \ \ 0 \le \iota_j \le 2 \ .$$

The condition for the ι_j's corresponds to the interior and boundary of a system in 4-dimensions. The number of different equivalent classes of states are:

$$\begin{aligned} 4 \text{ (both cells of the same type)} \quad &+ \quad (4 \cdot 3/2) \text{ (both cells different)} \\ &+ \quad 4 \text{ (one cell types)} \; + \; 1 \text{ (no cells)} \; = \; 15 \, . \end{aligned} \tag{5.12}$$

Remark 5.3. For example $\pi_{0,1,0,1}(t)$ is the probability that the system has one cell of type 1 (resistant to drug 1) and another cell of type 3 (resistant to both drugs). Conversely $\pi_{0,0,2,0}(t)$ is the probability that both cells are of type 2 (resistant to drug 2).

The notation

$$\vec{\imath} \; = \; (\imath_0, \, \imath_1, \, \imath_2, \, \imath_3) \, ,$$

will be used, along with variations, as needed. The initial probability distribution is

$$\pi_{\vec{\imath}}(0) = 0 \, , \;\; \text{for} \;\; 0 \leq \imath_0 \leq 1 \, , \;\; \text{and} \quad \pi_{2,0,0,0}(0) = 1 \, . \tag{5.13}$$

By the end of the treatment period T one expects that $\pi_{2,0,0,0}(T) \simeq 0$ meaning that any surviving cancer cells will be resistant to at least one of the drugs. The expected outcome is such that

$$\pi_{0,0,0,2}(T) \; + \; \pi_{0,0,0,1}(T) \; + \; \pi_{\vec{0}}(T) \; \simeq \; 1 \, , \quad \pi_{\vec{0}}(T) \; \equiv \; \pi_{0,0,0,0}(T) \; \gtrsim \; 0 \, ,$$

Before computing the evolution of the probabilities, we construct the *PGF* as

$$\Psi(t;\vec{x}) \; = \; \sum_{\vec{\imath} \neq \vec{0}} \pi_{\vec{\imath}}(t) \cdot \prod_{\imath_j \in \vec{\imath}} x_j^{\imath_j} \; + \; \pi_{\vec{0}}(t) \, . \tag{5.14}$$

Referring to the notational mapping in (5.11), the term corresponding with $\pi_{0,1,0,1}(t) = \pi_{18}$ has the power $x_1 \cdot x_3$. Conversely, probability function $\pi_{0,0,2,0}(t) = \pi_{15}$ has the power x_2^2. Combining these gives the expression for the *PGF* from (5.14)

$$\begin{aligned}\Psi \;=\; & \pi_{20}\cdot x_3^2 \,+\, 2\pi_{19}\cdot x_3\cdot x_2 \,+\, 2\pi_{18}\cdot x_3\cdot x_1 \,+\, 2\pi_{17}\cdot x_3\cdot x_0 \,+\, \pi_{15}\cdot x_2^2 \\ & +\, 2\pi_{14}\cdot x_2\cdot x_1 \,+\, 2\pi_{13}\cdot x_2\cdot x_0 \,+\, \pi_{10}\cdot x_1^2 \,+\, 2\pi_9\cdot x_1\cdot x_0 \,+\, \pi_5\cdot x_0^2 \,+ \\ & +\, \pi_4\cdot x_3 \,+\, \pi_3\cdot x_2 \,+\, \pi_2\cdot x_1 \,+\, \pi_1\cdot x_0 \,+\, \pi_0\,.\end{aligned} \tag{5.15}$$

This demonstrates the complexity of the *PGF* in the simplest non-trivial case of 2-drugs and 2-cells. In this expression only the probabilities π_j depend on t explicitly, so we can take the partial of Ψ with respect to t to obtain the differential equation

$$\frac{\partial\Psi(t;\vec{x})}{\partial t} \;=\; \sum_{\vec{\imath}\neq\vec{0}} \pi_{\vec{\imath}}{}'(t)\cdot\prod_{\imath_j\in\vec{\imath}} x_j^{\imath_j} \;+\; \pi_{\vec{0}}{}'(t)\,. \tag{5.16}$$

Then we use the Kolmogorov Forward Equations to replace the functions $\pi_j'(t)$ with just $\pi_j(t)$. Once this is done we can make (5.16) into a PDE for Ψ. The entire expression will not be written out, but let us consider the first two terms.

$$\pi_{20}'\cdot x_3^2 \;=\; \big(-\tau_3^2(2\pi_{19})-\tau_3^1(2\pi_{18})\big)\,x_3^2 \;=\; -x_3\partial_{x_2}\tau_3^2\cdot\pi_{19}\cdot x_3x_2 \;-\; x_3\partial_{x_1}\tau_3^1\cdot\pi_{18}\cdot x_3x_1\,.$$

Thus (5.16) can be expressed as

$$\partial_t\Psi \;\equiv\; \frac{\partial\Psi(t;\vec{x})}{\partial t} \;=\; L\Psi(t;\vec{x}) \;=\; \sum v_j(\vec{x})\,\frac{\partial\Psi(t;\vec{x})}{\partial x_j} \;=\; \vec{v}\cdot\nabla\Psi\,, \tag{5.17}$$

where L is a first-order linear partial differential operator *PDO* with variable coefficients $v_j(\vec{x})$ that are independent of t. The initial probabilities are stated in (5.13). Substituting these into (5.15) gives the Initial Conditions for the *PDE* in (5.17) to be

$$\Psi(0,\vec{x}) \;=\; x_3^2\,. \tag{5.18}$$

Note that all the probabilities vanish except for $\pi_{20}(0)=1$. Thus, to solve the *IVP* as

defined by (5.17) and (5.18) we employ the method of characteristics, and assume that $\vec{x} = \vec{x}(t)$. Then we can rewrite (5.17) as

$$\frac{d\Psi}{dt} \;=\; \vec{v}\cdot\nabla\Psi \;=\; 0\frac{\partial\Psi}{\partial t} \;-\; \vec{v}\cdot\nabla\Psi \;=\; 0\,. \tag{5.19}$$

The immediate solution to (5.19) is that $\Psi = constant$, as a function of t. Thus along a characteristic γ the *PGF* satisfies $\Psi|_\gamma = x_3^2$. Characteristic curves are found by solving the system of *ODEs*: $\vec{x}' = \vec{v}(\vec{x})$ using different Initial Conditions *IC*. The *IC* that $x_3(0) = 1$ and $0 = x_2(0) = x_1(0) = x_0(0)$ gives the probability of resistance over time. Since we are most interested in the value of $\pi_{\vec{0}}(T)$, the probability of the treatment being successful, we need to use the *IC* that $x_3(0) = x_2(0) = x_1(0) = x_0(0) = 0$.

5.2.1 Pathways for the Two Cell - Two Drug Example

The One Cell - Two Drug case reduces to the deterministic situation. The case of two cancer cells becomes more complicated, involving 21 different states. For example, both cells susceptible to both drugs, one cell susceptible to both but the other now resistant, one cell extinguished but the other resistant to both drugs, etc. The Kolmogorov Forward (differential) equation gives a system for the evolution of the probabilities. A sample equation is

$$\pi'_{0,1,0,1}(t) \;=\; -\kappa\pi_{0,1,0,1} \;-\; \tau_1\,\pi_{0,0,0,2} \;+\; \tau_2\,\pi_{1,0,0,1} \;+\; \tau_2\,\pi_{0,1,1,0}\,. \tag{5.20}$$

The quantity $\pi_{0,1,0,1}$ is the probability that one cell is resistant to drug 1, and the other cell is resistant to both. It decreases if a cell dies, at rate $\kappa > 0$ due to the chemotherapy (good), and it decreases at a rate $\tau_1 > 0$ due to mutations (bad). The probability will grow only due to transitions from other states at the rates τ_2 and τ_3. Solving the system, starting with $\pi_{\vec{I}}(0) = 0$ except $\pi_{\vec{0}}(0) = 1$, gives solutions similar to deterministic model, but the

interpretation is different.

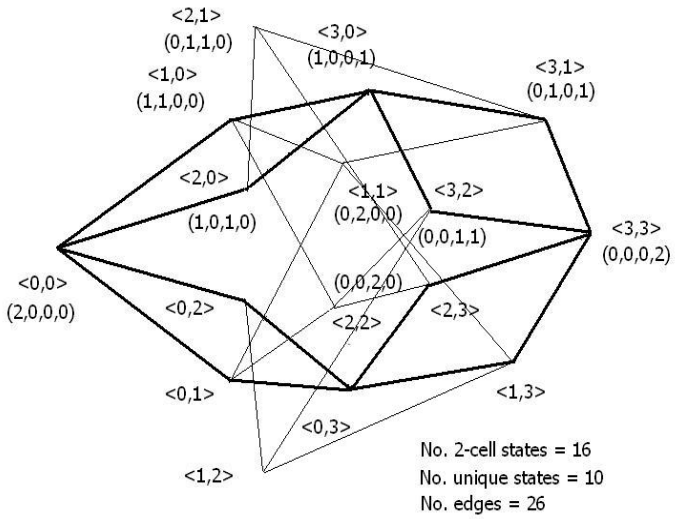

Figure 4 Schematic of various actual pathways.

Using a stochastic process allows us to compute the probability of having no cancer cells, within a time period $[0,T]$. This leads to a much more realistic model for the treatment of cancer using a cocktail of drugs. One obvious outcome of the model is that the objective of cancer-drug researchers to make κ large and τ small.

5.2.2 Solution to the Stochastic Differential Equations

There are three sets of equations to solve. The first are the *PDEs* for the probabilities $\pi_{\vec{I}}(t)$. The second is the equation $\dfrac{d\Psi}{dt} = 0$, and this implies that the initial form of $\Psi = x_{\vec{0}}^{N_0}$ holds for all time. Thus, although the *PGF* Ψ is independent of time, its components vary. They satisfy a system of *ODEs*

$$\frac{d\vec{x}}{dt} \;=\; -\vec{v}\,.$$

Solving these gives two quantities that change with time, $\pi_I(t)$ and $\vec{x}(t)$. Using equation (5.10), we construct the *PGF*. This allows us to compute the probability of having no cancer

cells, within a time period $[0,T]$,

$$P(I_{\vec{1}}=0) \;=\; \Psi(T,\vec{I}(T))\;.$$

This leads to a more realistic model for the treatment of cancer using a cocktail of drugs.

The quantity $\pi_{0,1,0,1}$ is the probability that one cell is resistant to drug 1, and the other cell is resistant to both. The probabilities with surviving cells decrease at rates $\kappa_i > 0$ due to the chemotherapy (good), but can increase at a rate $\tau_k^j > 0$ due to mutations (bad). The solutions to the equations in (5.10) are probabilities of the different states. A sample is

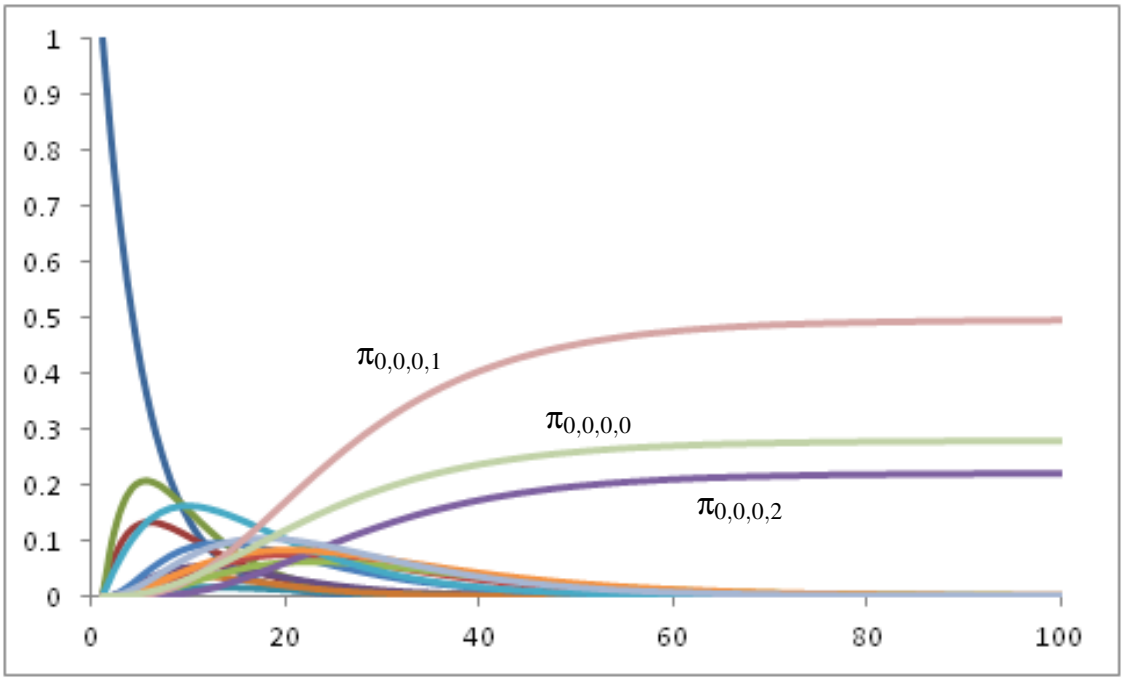

Figure 6. Numerical solutions $\pi_*(t)$ to the Kolmogorov Forward Equations.

Using the same parameters as in the deterministic case, there are three dominant possible outcomes, based on the probability distributions:

1) $\pi_{0,0,0,1}(100) \;\simeq\; 49.7\%$ (treatment partially successful).

2) $\pi_{0,0,0,0}(100) \;\simeq\; 27.9\%$ (remission achieved);

3) $\pi_{0,0,0,2}(100) \;\simeq\; 22.2\%$ (treatment unsuccessful);

The total is nearly 100% indicating that further use of the treatment will have little effect.

5.3 Product of Probabilities Approach

The stochastic differential equation approach just studied can be modified to consider cross interactions [7]. However, if the cells are truly indistinguishable, then the one-cell distributions, given in (5.9), can be combined giving the identity

$$1 \;=\; \left(\pi_{\langle 0\rangle} + \pi_{\langle 1\rangle} + \pi_{\langle 2\rangle} + \pi_{\langle 3\rangle} + \pi_{\emptyset}\right)^2 \,. \tag{5.22}$$

This has 25 separate terms. However the number of duplicates are $(5 \cdot 4/2) = 10$. Thus there are only 15 different states. By writing programs for each case using $\Delta t = 1$ and considering the values at $t = 100$ we can compare the difference between the two methods, summarized below.

Probs:	π 0002	π 0001	π 0000
Stochastic DE	0.221708	0.497365	0.27894
Product Approach	0.225105	0.497831	0.275245
Relative % Difference	1.5	0.1	1.3

Table 1: Comparison between stochastic (KFE) approach, and product approach.

The agreement of the two approaches is due to the fact that evolution of each cancer cell is considered to be independent in this thesis. However, this is not the case in-vivo, so the stochastic differential equation approach would have the be modified. The theory is now in place to consider more difficult, but realistic situations.

5.4 Higher-Order Stochastic Cases

We briefly consider the next order cases to demonstrate the increase in complexity associated with stochastic modeling. Independence of cells will still be assumed here.

5.4.1 2-drugs and N-cells

In the 2-drug case, there are 2^2+1 different states represented by the numbers (used as indices) $\{0,1,2,3,\emptyset=4\}=\mathbb{Z}_5$. When there are N different cancer cells, the system will have 5^N possible configurations. However, if these cells are considered to be independent, then the number unique configurations decreases. We can understand this by first letting $\iota_j(t)$ denote the number of cells in state $j\in\mathbb{Z}_5$, at any time t. Then we can construct the vector

$$\vec{\iota}(t) \;=\; (\iota_0,\iota_1,\iota_2,\iota_3,\iota_4)\;,$$

and impose the restrctions that

$$\#(\vec{\iota}) \;\equiv\; \iota_0+\iota_1+\iota_2+\iota_3+\iota_4 \;=\; N \qquad \text{and} \qquad 0\le\iota_j\le N\;.$$

Now we have to choose 5 different whole numbers from N in such a way that the total is N. To do this, consider a string of $N+4$ numbers where one chooses 4. The 4 choices breaks the string of N numbers into 5 parts. The first part counts to ι_0. The second to ι_1, and so on. This gives, [9]

$$\text{Unique states for } N \text{ cells in 2-drug environment} \;=\; \binom{N+4}{4}\;. \tag{5.23}$$

Example 5.4. The two-drugs and two-cells gives $\#(\vec{\iota})=2=N$ and the number of distinct states are $\binom{6}{4}=15$, which was already determined in (5.12). The two-drug and three-cell case has $\#(\vec{\iota})=3$ which results in the number of distinguishable states to be

$$\begin{aligned} 4 \text{ (three cells of the same type)} \quad &+ \quad (4\times 3) \text{ (two the same, one different)} \\ &+ \quad (4\times 3\times 2/3!) \text{ (all three different)} \\ 10 \text{ (two cells)} \quad &+ \quad 4 \text{ (one cell)} \;+\; 1 \text{ (no cells)} \;=\; 35\;. \end{aligned}$$

However, from (5.23) one quickly obtains $\binom{7}{4}=35$ distinct states.

5.4.2 m-drugs and N-cells

Finally, when there are m drugs used, then there are $2^m - 1$ ways to be resistant to at least one of the drugs. Otherwise, there is the state of susceptibility to all drugs, and the state of no cells. This gives a total of $2^m + 1$ states. We can index the single cell states as

$$\text{Unique states for } N\text{-cells in } m\text{-drug environment } = \binom{N+2^m}{2^m}. \tag{5.24}$$

Thus, in the special case of 3-drugs and 2 cells there are $\binom{2+2^3}{2^3} = \binom{10}{8} = 45$ cases.

CHAPTER 6: Conclusions

In many systems, a deterministic approach is sufficient to understand future behavior. However, for complex systems with many pathways, a stochastic approach leads to more realistic estimates of outcomes. In particular, this approach to modeling the progress of treatments allows for meaningful results, like the probability of achieving remission. Research into the stochastic method of predicting outcomes gives a way to analyze the drug-effectiveness parameters that can be measured and adjusted for optimality. As the use of multiple drugs during a single treatment becomes the norm, these methods will need to be further refined.

CHAPTER 7: APPENDIX I

Comparison between Euler Method and *RK2* It was observed that there is not a significant difference between Euler's method and Runge-Kutta of order 2. The programs were written in EXCEL. We only show the results for $N(t)$.

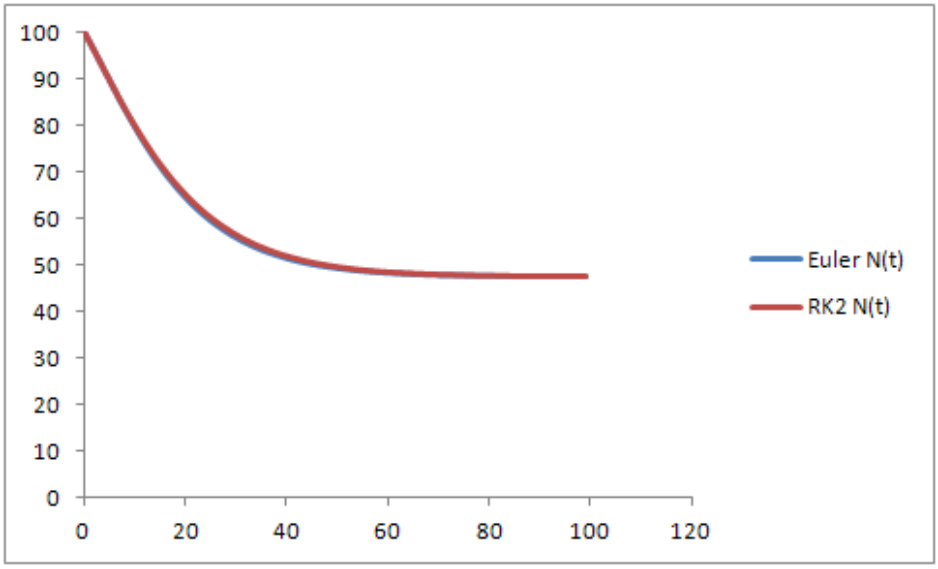

Figure 7. Numerical solutions using Euler and *RK2* methods.

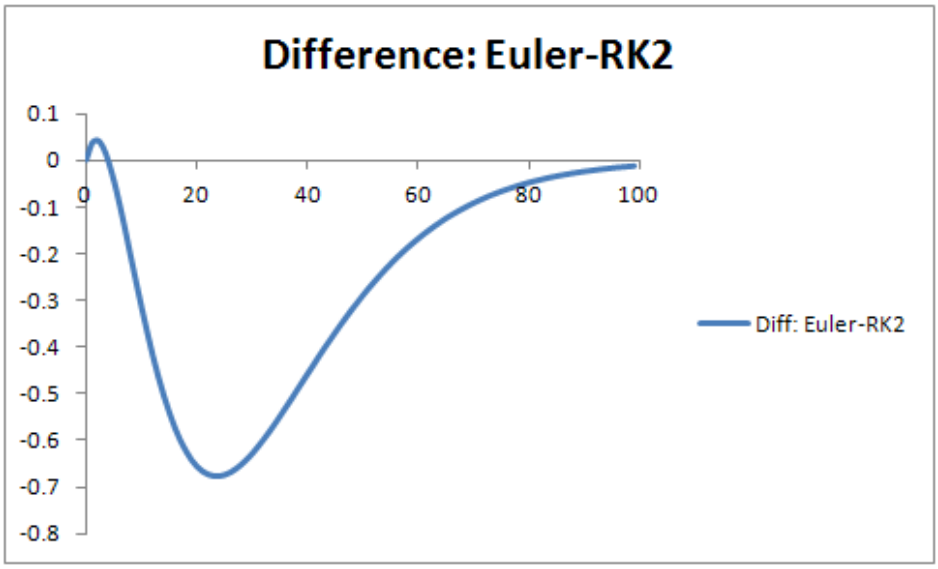

Figure 8. Differences for the Euler and *RK2* numerical methods.

CHAPTER A: APPENDIX II

The following were programmed in EXCEL and used to produce Figure 6:

Pi 2000 = B2+(-2*$S$3*B2-2*$V$3*B2-2*$X$3*B2)*$Z$3

Pi 1100 = C2+(2*$V$3*B2-($V$3+$X$3+$W$3)*C2-($S$3+$T$3)*C2)*$Z$3

Pi 1010 = D2+(2*$X$3*B2-($S$3+$U$3)*D2-($V$3+$X$3+$Y$3)*D2)*$Z$3

Pi 0110 = E2+($X$3*C2+$V$3*D2-($W$3+$Y$3)*E2-($T$3+$U$3)*E2)*$Z$3

Pi 0200 = F2+($V$3*C2-2*($T$3+$W$3)*F2)*$Z$3

Pi 0020 = G2+($X$3*D2-2*$Y$3*G2-2*$U$3*G2)*$Z$3

Pi 1001 = H2+($W$3*C2+$Y$3*D2-$S$3*H2-($V$3+$X$3)*H2)*$Z$3

Pi 0011 = I2+($W$3*E2+2*$Y$3*G2+$X$3*H2-$U$3*I2-$Y$3*I2)*$Z$3

Pi 0101 = J2+($Y$3*E2+2*$W$3*F2+$V$3*H2-$T$3*J2-$W$3*J2)*$Z$3

Pi 0002 = K2+($W$3*J2+$Y$3*I2)*$Z$3

Pi 1000 = L2+($S$3*(2*B2-L2)+$T$3*C2+$U$3*D2-($V$3+$X$3)*L2)*$Z$3

Pi 0100 = M2+($S$3*C2+2*$T$3*F2+$U$3*E2+$V$3*L2-$W$3*M2-$T$3*M2)*$Z$3

Pi 0010 = N2+($S$3*D2+$T$3*E2+2*$U$3*G2+$X$3*L2-$Y$3*N2-$U$3*N2)*$Z$3

Pi 0001 = O2+($S$3*H2+$T$3*J2+$U$3*I2+$W$3*M2+$Y$3*N2)*$Z$3

Pi 0000 = P2+($S$3*L2+$T$3*M2+$U$3*N2)*$Z$3

Total = B3+C3+D3+E3+F3+G3+H3+I3+J3+K3+L3+M3+N3+O3+P3

Decay — Transition Params —- Delta t

k0 k1 k2 — t01 t13 t02 t23

0.02 0.03 0.04 — 0.03 0.04 0.05 0.06 — 1

pi 0002 pi 0001 pi 0000 — Total

0.221708 0.497365 0.27894 — 0.998013

Table 1: Two-drug, two-cell stochastic solution

Time	pi 2000	pi 1100	pi 1010	pi 0110	pi 0200	pi 0020	pi 1001	pi 0011	pi 0101	pi 0002	pi 1000	pi 0100	pi 0010	pi 0001	pi 0000	Total
1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
2	0.8	0.06	0.1	0	0	0	0	0	0	0	0.04	0	0	0	0	1
3	0.64	0.0978	0.16	0.006	0.0018	0.005	0.0084	0	0	0	0.0738	0.0024	0.004	0	0.0008	1
4	0.512	0.11957	0.192	0.0147	0.0045	0.012	0.0211	0.0013	0.0008	0	0.1014	0.0068	0.01107	0.000504	0.002508	1
5	0.4096	0.12997	0.2048	0.0239	0.0074	0.0192	0.0353	0.0042	0.0026	0.0001	0.123	0.0126	0.02027	0.00193272	0.00518	1
6	0.3277	0.13245	0.2048	0.0325	0.0103	0.0256	0.0492	0.0088	0.0055	0.0005	0.1391	0.0194	0.03074	0.004602732	0.008827	1
7	0.2621	0.12959	0.1966	0.0397	0.0128	0.0307	0.0619	0.0148	0.0093	0.0012	0.1505	0.0268	0.04174	0.008723998	0.013421	1
8	0.2097	0.12329	0.1835	0.0454	0.0149	0.0344	0.0727	0.0217	0.014	0.0025	0.1577	0.0344	0.05268	0.014408064	0.018904	1
9	0.1678	0.11491	0.1678	0.0493	0.0165	0.0367	0.0814	0.0291	0.0191	0.0043	0.1613	0.0419	0.06308	0.021681745	0.025195	1
10	0.1342	0.10545	0.151	0.0517	0.0177	0.0377	0.0879	0.0366	0.0245	0.0068	0.1621	0.049	0.07261	0.03050295	0.032201	1
11	0.1074	0.09557	0.1342	0.0527	0.0184	0.0377	0.0924	0.0439	0.0299	0.01	0.1604	0.0557	0.08104	0.040776566	0.039818	1
12	0.0859	0.08577	0.1181	0.0526	0.0187	0.0369	0.095	0.0508	0.0352	0.0138	0.1569	0.0617	0.08825	0.052369198	0.047939	1
13	0.0687	0.07634	0.1031	0.0515	0.0186	0.0354	0.096	0.057	0.0402	0.0183	0.152	0.0671	0.09416	0.065122115	0.05646	1
14	0.055	0.06749	0.0893	0.0496	0.0183	0.0335	0.0957	0.0624	0.0449	0.0233	0.1459	0.0716	0.09878	0.078862166	0.065277	1
15	0.044	0.05931	0.077	0.0472	0.0178	0.0313	0.0942	0.067	0.0491	0.0289	0.1391	0.0754	0.10216	0.093410642	0.074296	1
16	0.0352	0.05187	0.066	0.0445	0.0171	0.0289	0.0917	0.0706	0.0527	0.0349	0.1318	0.0785	0.10436	0.108590229	0.083428	1
17	0.0281	0.04516	0.0563	0.0415	0.0162	0.0264	0.0886	0.0734	0.0558	0.0412	0.1243	0.0808	0.10548	0.124230229	0.092593	1
18	0.0225	0.03917	0.0479	0.0384	0.0153	0.0239	0.0849	0.0753	0.0583	0.0478	0.1166	0.0824	0.10562	0.14017032	0.10172	1
19	0.018	0.03386	0.0405	0.0353	0.0143	0.0215	0.0809	0.0764	0.0603	0.0547	0.1089	0.0833	0.10491	0.15626307	0.110747	1
20	0.0144	0.02919	0.0342	0.0322	0.0133	0.0193	0.0766	0.0768	0.0618	0.0617	0.1014	0.0837	0.10346	0.172375441	0.119622	1

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